

## On redisorganisation

*As soon as we abandon our own reason, and are content to rely upon authority, there is no end to our troubles.* That is a quote from Bertrand Russell taken from a work called "An Outline of Intellectual Rubbish". Bandolier hasn't read it in full, in part because philosophy makes what little brain we have hurt. But when it comes to managing organisations, a little brain goes a long way.

Or it should do. The golden rule that operates 99.99% of the time is that if it ain't broke, don't fix it. Most organisations ain't broke, but they always need tinkering with to make them run better. To tinker here means to upgrade, nurture, enhance, or develop rather than the several less positive dictionary definitions.

Understatement is the name of the game in management, together with recognising that every employee is a manager, making decisions crucial to the success of the firm, and giving them the tools to do a better job. Relying on big brother (authority) to make all the decisions results in an organisation of jobsworths, doomed to failure.

Healthcare around the world is undergoing massive reorganisation, often using organisational theories, but sometimes because reorganisation makes it look as if someone is doing something. A systematic review has looked for the evidence [1].

## Fantasy and reality

Actually, this is not a systematic review, but a diatribe about continued, ongoing, pointless, redisorganisation, without a jot or tittle of evidence that any of it ever does any good, or has ever done any good. The evidence found was fantasised, but as the authors say, though their fantasies may well resemble other people's realities, that isn't their fault.

The most common reason for repeated reorganisations is that there isn't one. Trillions of dollars, more even than Bandolier's piggy bank, is spent each year on this activity, without much evidence of benefit. Success is measured in large consultancy fees.

Most people would rather die than think. Thinking about the many redisorganisations in healthcare would make most sensible people weep, which makes not thinking about it the preferable option. Read this paper, and make others read it too. If nothing else, it will make you laugh out loud at the utter folly of spending huge sums on reorganisation while missing the simple things that could make a difference. It

might just jolt you back to reality, and make you think about what is happening around you. You won't like it, but much good medicine has a nasty taste.

And it is worth remembering the old axiom, that the trouble with the world is that the stupid are cocksure and the intelligent full of doubt.

## Missing the obvious

There is a secret magic in numbers, and while some take great pleasure in prime or perfect numbers, Bandolier has a dread of small numbers. Small numbers in our world means that the random play of chance can blow chill and strong to bury the truth. The theme of limited evidence continues in this issue with a series of systematic reviews or studies which, however good, are limited by low numbers of events, with resulting uncertainty.

How we deal with that uncertainty is situation dependent. For instance, a finding that anti-TNF agents produce fewer cardiovascular events in rheumatoid arthritis is a good thing, fantastic for a condition with a higher rate than normal. Even though the numbers are small, we feel relaxed about it. But what if it were the other way around, and there were more? Think of the hype and headlines that would follow, even on the same limited numbers.

Natural history studies are rare as hens' teeth. One tries to chart spontaneous clearance of hepatitis C virus in a number of small studies. It raises as many, or more, questions than it answers, but it really demonstrates how variable doing nothing can be when numbers are small.

### Reference:

- 1 AD Oxman et al. A surrealistic mega-analysis of reorganisation theories. *Journal of the Royal Society of Medicine* 2005 98: 563-568.

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# ALCOHOL CONSUMPTION AND AF

Bandolier loves a mystery, or the appearance of a mystery. Several readers have asked about links between behaviour and atrial fibrillation (AF), specifically about exercise and alcohol. For exercise there seems little direct linkage of prior exercise leading to future AF (though others may know better). For alcohol, the situation is different, in those who imbibe too freely or too well.

The first references linking high alcohol consumption and AF were from Poland in the late 1960s, but the holiday heart syndrome was defined in 1978 [1] as:

*An acute cardiac rhythm and/or conduction disturbance associated with heavy ethanol consumption in a person without other clinical evidence of heart disease, and disappearing, without evidence residual, with abstinence.*

That may be a short-term poisoning effect, and is not quite the same as effects over the longer term related to habitual high alcohol consumption. Bandolier has examined some of the recent literature found in a quick search. Three observational studies come to much the same conclusion. In what follows Bandolier is giving alcohol consumption as grams per day; 10 grams is about what is found in a 330 mL bottle of beer, which is about one unit.

## Framingham study [2]

This detailed, prospective, long-term study of a cohort of 10,333 Americans had 1,055 cases of AF and 4,672 controls free of AF. The average age was 45 years at baseline. Patients with AF had significantly greater rates of hypertension, myocardial infarction, heart failure, hypertrophy, valvular disease and diabetes.

Rates of AF were calculated at different levels of daily alcohol consumption, with relative risk compared to no alcohol consumption. For women and men separately there was no significant increased risk at any level of consumption, but there was a trend to greater risk at higher consumption (Figure 1 shows this for men). Combining data for both men and women, the relative risk was significantly higher at highest alcohol consumption, with a relative risk of 1.3 (95% CI 1.01 to 1.78). Risk calculations were adjusted for various possible confounding factors.

## Danish study [3]

This Danish study was large, with 50,000 people aged 50-64 years at baseline contributing information, and long, with an average duration of follow up of about 5.8 years. Over this time the incidence of AF was 1.7% in men (29 per 10,000 person years; 3 per 1,000 per year) and 0.7% in women (12 per 10,000 person years; 1 per 1,000 per year). Almost 80% of women consumed 20 grams of alcohol per day or less, while 50% of men consumed 20 grams of alcohol per day or more.

This analysis used quintiles of alcohol consumption. For women the highest quintile consumed an average of 39

Figure 1: Relative risk of AF in men by daily alcohol consumption (Framingham)

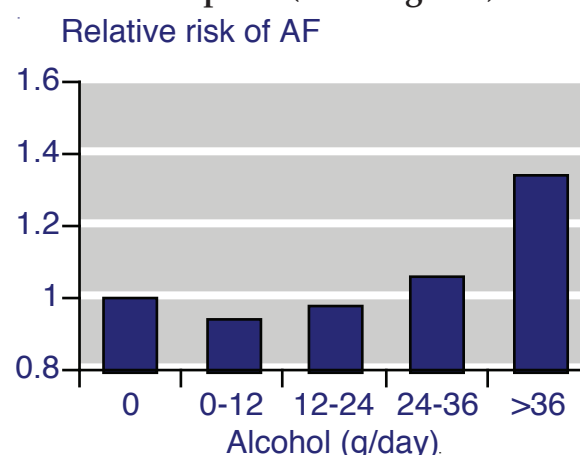


Figure 2: Relative risk of AF in men by daily alcohol consumption (Denmark)

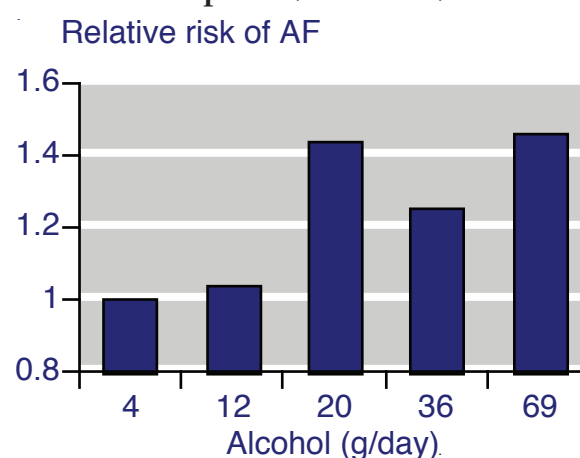
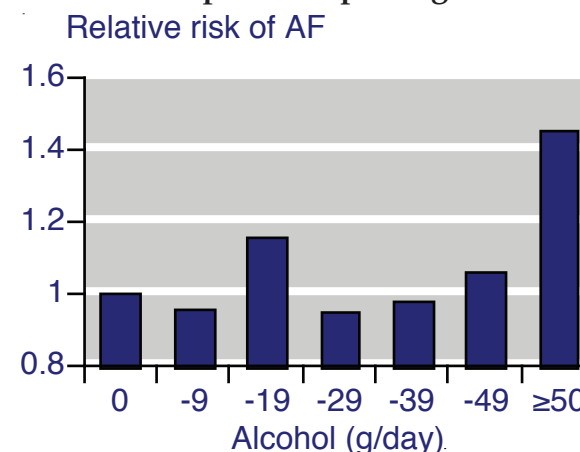


Figure 3: Relative risk of AF in men by daily alcohol consumption (Copenhagen)



grams of alcohol per day. There was no significant association between alcohol consumption and AF for women. For men the highest quintile consumed an average of 69 grams of alcohol per day. There was a significant association between alcohol consumption and AF for men (Figure 2). At the highest level of consumption the adjusted relative risk was 1.5 (1.1 to 2.0).

## Copenhagen study [4]

Another, but different, study from Denmark, used a randomly drawn sample of the population of Copenhagen,

and analysed 16,400 individuals. The average age was 50 years. Almost all women (90%) consumed 20 grams or less of alcohol daily (two drinks a day), while two-thirds of men consumed more than 20 grams a day. This long-term study had an average of 17 years of follow up.

The analysis here was by different levels of alcohol intake. For women, the highest level of intake was 29 grams daily or above. There was no significant association between alcohol consumption and AF for women. For men, there were six groups; the highest was 50 grams daily or more. There was a significant association between alcohol consumption and AF for men (Figure 3). At the highest level of consumption the adjusted relative risk was 1.5 (1.02 to 2.0).

## Comment

AF has been associated previously with alcohol abuse [1,5], with a doubling of risk at alcohol consumption above 42 units a week, or about 60 grams daily (more than six bottles of beer a day). These three studies would seem to confirm that in men, long-term consumption of about 40 grams of alcohol a day (four units or more, four bottles of beer or more) is associated with an increase in risk by about 30% to 50%. They also show a dose response relationship.

Demonstrating any effect in women is more difficult because few women drink enough. In the studies, most women consumed two drinks a day (bottles of beer, moderate glasses of wine) or less. In consequence there were few drinking sufficient to demonstrate an effect. That does not mean, though, that the laws of physiology do not apply to women. The absence of any evidence is not evidence of no effect at higher alcohol intakes.

Having a holiday heart flutter of the non-romantic sort after drinking more than usual is probably signalling that too much alcohol is damaging that particular heart. What we are seeing is a dose response relationship, because moderate alcohol intake has been shown to produce less heart failure than no alcohol [6]. The message is to cut down, probably to no more than one or two drinks a day. Quality rather than quantity, perhaps.

### References:

- 1 PO Ettinger et al. Arrhythmias and the "Holiday Heart": alcohol-associated cardiac rhythm disorders. *American Heart Journal* 1978 95: 555-562.
- 2 L Djoussé et al. Long-term alcohol consumption and the risk of atrial fibrillation in the Framingham study. *American Journal of Cardiology* 2004 93: 710-713.
- 3 L Frost, P Vestergaard. Alcohol and risk of atrial fibrillation or flutter. *Archives of Internal Medicine* 2004 164: 1993-1998.
- 4 KJ Mukamal et al. Alcohol consumption and risk of atrial fibrillation in men and women. *Circulation* 2005 114: 1736-1742.
- 5 A Ruigomez et al. Incidence of chronic atrial fibrillation in general practice and its treatment pattern. *Journal of Clinical Epidemiology* 2002 55: 468-473.
- 6 JL Abramson et al. Moderate alcohol consumption and risk of heart failure among older persons. *JAMA* 2001 285: 1971-1977.

## THE CASE FOR CHOCOLATE

Bandelier obviously has chocolate lovers among its readers, but chocolate lovers who want a healthy lifestyle. Can it really be true, they ask, that chocolate can be good for you? Andrew's mother's hairdresser's friend is of the opinion that a little of what you fancy does you good, but here a systematic review [1] promised some evidence to support any prejudices.

First a note on chocolate. It is made from cocoa beans that are fermented, roasted and cracked to leave a kernel, which is ground to a paste. If hardened, this is bitter chocolate. Adding sugar and cocoa butter produces dark chocolate, and the addition of this to milk concentrate produces milk chocolate. Cocoa butter and milk concentrate contain fats, a large proportion of which is (saturated) stearic acid. Chocolate also contains theobromine and caffeine, and particularly antioxidant flavanoids, procyanadins, and flavenols. These antioxidants are considered to have significant protective effects against heart disease.

## Systematic review

The search was limited to English language studies found in MEDLINE to mid-2005, which examined at least one of several aspects of the relationship between chocolate and cardiovascular health.

## Results

The review covered about 140 publications and looked at several different aspects.

### Stearic acid

Observational studies of stearic acid (dietary, or serum levels) generally show that it is associated with higher levels of heart disease, either as incidence or mortality. Stearic acid comes predominantly from meat and dairy products, so there is little surprise there. Stearic acid from chocolate is a small contributor to stearic acid intake, of about 5% in the average western diet.

### Flavenoids in chocolate

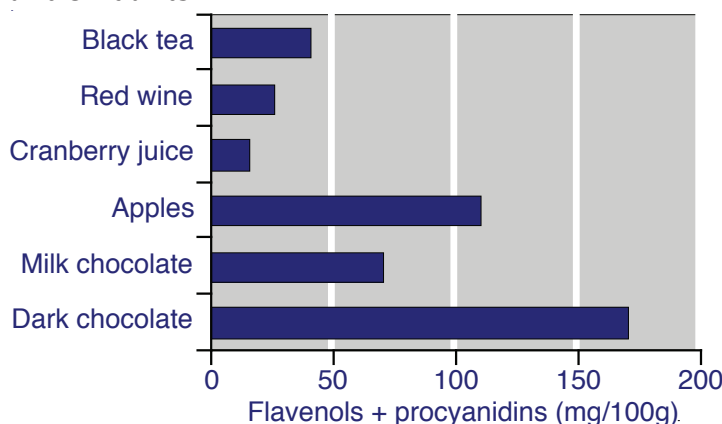
Chocolate, dark or milk, has higher levels of flavenoids or oxygen radical absorbance capacity than almost any other food, based on weight (Figures 1 and 2) or on energy. Only apples come close.

### Chocolate and mechanisms

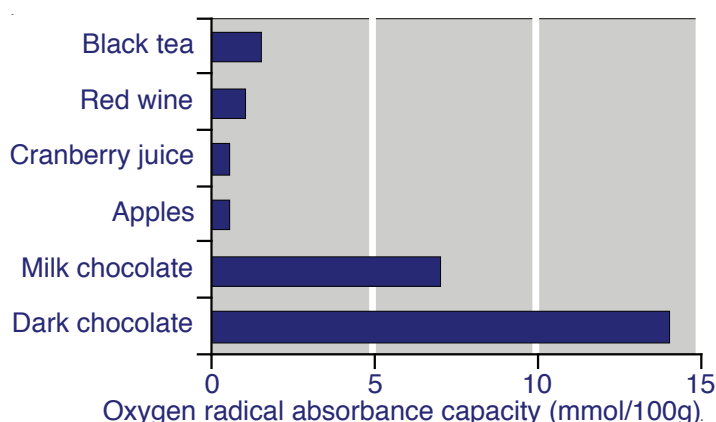
Over 20 small trials have studied effects of chocolate on physiological and biochemical parameters over the short term. The quality of the studies and the magnitude of the effects cannot be seen from the review. Several reported lower blood pressure, decreased low density cholesterol oxidation, decreased platelet aggregation, improved endothelial function, and greater antioxidant capacity.



**Figure 1: Flavenol and procyanadin content of chocolate compared with other foods high in antioxidants**



**Figure 2: Oxygen radical absorbance capacity of chocolate compared with other foods high in antioxidants**



## Flavonoids and heart disease

The review reports 11 prospective observational studies of the association between flavonoid consumption and heart disease or stroke. Studies were conducted in populations of 500 to 40,000 (about 190,000 people in total), followed up for 5 to 28 years. Most reported some reduction in coronary heart disease mortality. A meta-analysis indicated a significant protective effect between flavonoid consumption and risk of coronary heart disease mortality, with a relative risk of 0.81 (95% confidence interval 0.71 to 0.92).

## Comment

Many different polyphenols contribute to antioxidants in the diet. There is no absolute need to eat chocolate to get antioxidants. But chocolate has lots of them, and different ones, and is pretty nice on the whole for most of us. Eating too much chocolate is not a good idea, though, because of the sugar and stearic acid it contains. Like so many other things, a little chocolate taken regularly is likely to be a good thing; a little of what you fancy.

Reference:

- 1 EL Ding et al. Chocolate and prevention of cardiovascular disease: a systematic review. *Nutrition & Metabolism* 2006 3:2 (online journal: [www.nutrition-and-metabolism.com](http://www.nutrition-and-metabolism.com))

## ANTI-TNF AND CARDIOVASCULAR DISEASE

Rare but serious adverse events are difficult to measure in randomised trials. When rates of such events are below 1 in 100, and especially 1 in 1000, conventional trials of a few hundred patients or fewer are usually insufficiently large for even a single event to reliably be captured. Consequently we rely on observational studies.

Prospective evaluations of patients treated with new medicines in registers are unusual. Bandolier 104 discussed one such for anti-TNF therapy in rheumatoid arthritis: it gave the same efficacy result as meta-analysis of randomised trials. A new report [1] follows up, but rather than reporting an unexpected adverse event, it records an unexpected benefit.

## Study

The study was based in southern Sweden, on a register of patients treated with anti-TNF agents, and a community-based cohort within the same geographical area, largely before the introduction of the agents. There were, therefore, two cohorts, those exposed and those not exposed to anti-TNF therapies. The exposed cohort was based on a population of 1.3 million, and included all patients with rheumatoid arthritis treated with anti-TNF agents, between early 1999 and end 2001. The unexposed cohort was from the southern Swedish city of Malmö with a population of 0.3 million, from mid-1997.

Patients in the cohorts had to be free of pre-existing cardiovascular disease. Outcome was a new cardiovascular disease event during the study period, without a previous event in the preceding 10 years. Information on cardiovascular events came from national discharge and death registries, in which discharge diagnoses and causes of death have been verified as accurate.

## Results

Patients in both groups were mainly (76%) women, with an average age of 58 years. Those treated with anti-TNF agents tended to have greater initial disease severity in terms of global assessment, pain, and health assessment scores, and a much higher proportion of treated patients had received previous prednisolone treatment (75% compared with 22%) and more disease modifying drugs.

There were fewer cases of first cardiovascular disease event with anti-TNF treatment (Table 1), occurring in 1 in 71 exposed patients compared with 1 in 29 unexposed. The age, sex, and disability adjusted incidence rate was significantly reduced, with a relative risk of 0.5 (0.3 to 0.9). Several different analyses, for instance over the time the cohorts overlapped, or by various markers of severity, reached much the same result, as did excluding some cardiovascular disease endpoints, like heart failure.

There were also fewer cardiovascular deaths (Table 1). Age and sex adjusted rates were 1 in 450 for exposed, and 1 in

**Table 1: First cardiovascular disease events and mortality in rheumatoid arthritis patients exposed and not exposed to anti-TNF agents**

	Anti-TNF	
	Exposed	Not exposed
Number	531	543
Patient years	656	2056
Cardiovascular disease		
Cases (n)	13	85
Age, sex incidence	14	35
Cardiovascular death		
Cases (n)	2	12
Age, sex incidence	2.2	4.9
All-cause death		
Cases (n)	3	29
Age, sex incidence	3.2	12

Incidence is corrected for age and sex, and reported as the number of cases per 1000 patient years

200 for unexposed). All-cause deaths were also lower, with age and sex adjusted rates of 1 in 310 and 1 in 84 respectively. The number of deaths was small, though.

**Comment**

This is good news. Anti-TNF agents, while expensive, produce excellent results in appropriate rheumatoid arthritis patients. The implication that they probably produce additional, perhaps unexpected, benefits, is welcome. The figures suggest that anti-TNF therapy for one year reduces new cardiovascular events by an absolute 2%, or a one-year NNT of 50. If that were maintained over the longer term, a 10-year NNT of 5 would be better than statins in someone with a 30% 10 year cardiovascular risk. Moreover, the authors show that the standardised mortality rate with anti-TNF treatment was the same as that for the background population of Malmö.

The problem is numbers. We have only 13 cases of cardiovascular events with TNF therapy, and this, however good, is an observational study. Without supporting evidence we must be cautious about extolling this potential benefit.

It is interesting to reflect on the reaction to these results had they been the other way around, and we were reporting more cardiovascular events, rather than fewer. Caution should still have been the watchword, but what the reaction would have been, despite the tremendous benefits of anti-TNF therapy, is a different question for another day.

Reference:

1 LT Jacobsson et al. Treatment with tumor necrosis factor blocker is associated with a lower incidence of first cardiovascular events in patients with rheumatoid arthritis. *Journal of Rheumatology* 2005 32: 1213-1218.

**DIABETES AND CONGENITAL ABNORMALITIES**

Because there are so many things to know, it is hardly surprising that all of us don't know much. Bandolier had no inkling, for instance, that mothers with diabetes had a higher risk of having children with congenital abnormalities. A new study [1] estimates the frequencies, and tells us some of the problems.

**Study**

Since 1982 in Hungary it has been compulsory to register all congenital abnormalities. It is a thorough and comprehensive system. Cases were children identified with serious congenital abnormality from 1980 to 1996, with, for each, two newborn children without congenital abnormality as controls. In each case questionnaires were sent to mothers about maternal health, drugs, and pregnancy complications, and district nurses questioned all non-responding case families and control families. Diabetes was defined as use of insulin during or before the first trimester.

**Results**

There were 22,843 cases, of whom 63 (0.3%) were born to mothers with pre-gestational insulin-treated diabetes. Among 38,151 controls, there were 50 diabetic mothers (0.1%). Before and after adjustment for possible confounding factors, the odds ratio was 2.1 (95% CI 1.5 to 3.1). No mothers had taken antiepileptic drugs.

The 63 cases comprised a range of different serious congenital abnormalities. The largest group was cardiovascular, followed by multiple congenital abnormalities, and hypospadias; together these comprised 36 of the 63 cases, and for most specific conditions there were four or fewer cases.

**Comment**

The organisation of a countrywide register like this is an enormous undertaking, as is the organisation of surveillance and analysis. Yet even such an undertaking identified only 63 congenital abnormalities in children of diabetic mothers. Our best guess is that the rate is doubled in diabetes across a basket of different serious congenital abnormalities.

The paper notes that the four largest studies published previously comprised 25, 28, 59, and 75 congenital abnormalities in children of women with pre-gestational insulin-dependent diabetes. What we cannot say, because of the nature of the case-control design, is what is the absolute risk of a serious congenital abnormality for women with pre-gestational diabetes. All we can say is that it is twice as high as for women without diabetes.

Reference:

1 GL Nielsen et al. Risk of specific congenital abnormalities in offspring of women with diabetes. *Diabetes Medicine* 2005 22: 693-696.

# MELATONIN FOR SLEEP DISORDERS

Bandolier 82 looked at a good, large, randomised trial of melatonin for jet lag and found it not to be effective for sleep problems. Of course, melatonin may still have been useful for other sleep disturbances, though one would have had to be an enthusiast to bet on it. We now have two systematic reviews [1,2] to demonstrate that being a bit suspicious was probably the correct approach.

## Searching

These linked reviews had a heroic searching strategy, covering electronic searching of more databases than most of us knew existed, plus bibliographies and some hand searching. The latest searches were in early 2004. For inclusion, studies had to be randomised trials involving humans with a sleep disorder (primary, secondary, or sleep disorder accompanying sleep restriction), compared melatonin with placebo, and reported one or more of a variety of sleep outcomes. Primary sleep disorders were those for which there was no medical condition (schizophrenia, developmental disability, depression) causing it. Studies reporting only adverse events were also included for safety analysis.

### Primary sleep disorder [1]

Fourteen trials were included for efficacy and 10 for safety. Trial size ranged from 16 to 62 patients. The maximum number of patients upon which efficacy was based was 425, and for safety 281.

There was no difference between melatonin and placebo for all efficacy outcomes except sleep onset latency, which was 12 minutes less with melatonin, with a 95% confidence interval of 5 to 18 minutes. The 10 studies of better reporting quality and less likelihood of being biased were not significantly different for sleep latency. There was no difference in adverse event rates for headache, dizziness, nausea, or drowsiness.

### Secondary sleep disorder [2]

For sleep disorder secondary to another medical condition, nine trials were included for efficacy and seven for safety. Trial size ranged from six to 157 patients. The maximum number of patients upon which efficacy was based was 382, and for safety 253.

There was no difference between melatonin and placebo for sleep onset latency, wakefulness after sleep onset, or minutes of restless eye movement sleep. There was a small (16 minute) significant increase in total sleep time. There was no difference in adverse event rates for headache, dizziness, nausea, or drowsiness.

### Sleep restriction [2]

For sleep restriction studies, nine trials were included for efficacy and 10 for safety. Trial size ranged from 17 to 320 patients. The maximum number of patients upon which efficacy was based was 508, and for safety 560.

Table 1: Summary of results of trials of melatonin for sleep disorders

Sleep disorder	Number of patients		Conclusion
	Melatonin	Placebo	
Primary	218	207	No effect on any outcome using better quality studies
Secondary	220	162	Increased sleep time by about 16 minutes
Sleep restriction	309	199	Increased sleep time by about 18 minutes, based on a subgroup of only 200 patients

There was no difference between melatonin and placebo for sleep onset latency, wakefulness after sleep onset, or minutes of restless eye movement sleep. There was a small (18 minute) increase in total sleep time, based on a small number of patients. There was no difference in adverse event rates for headache, dizziness, nausea, or drowsiness.

## Comment

Different doses of melatonin were given to different patients for different periods of time, and while similar outcomes were reported, this was not consistent throughout the studies. Most trials were trivially small. There was no obvious dose response. Any benefits for melatonin were small (Table 1), and derived from multiple comparisons. What is the likelihood of melatonin being a whizzo medicine for sleep disorders? Not likely, is it?

In each review subgroup analysis with tiny numbers makes one worry. Is melatonin safe for short term use? Using the rule of three, we can only conclude that since no disaster has been seen in about 700 patients taking melatonin, we can be 95% sure that disasters will not occur more frequently than once in every 200 patients taking melatonin.

There is a call for large-scale randomised trials to prove the lack of efficacy of melatonin conclusively. Given the costs and difficulties of clinical research, and given that there is no whisker, no sniff of any useful efficacy, and given the unknown quantity of unpredictable but possibly harmful effects, is it ethically sound or reasonable for more trials, at least in these conditions?

References:

- 1 N Buscemi et al. The efficacy and safety of exogenous melatonin for primary sleep disorders: A meta-analysis. *Journal of General Internal Medicine* 2005 20: 1151-1158.
- 2 N Buscemi et al. Efficacy and safety of exogenous melatonin for secondary sleep disorders and sleep disorders accompanying sleep restriction: meta-analysis. *BMJ* 2006 doi:10.1136/bmj.38731.532766.F6 (published 10 February 2006).



# FIBRE FOR HAEMORRHOID COMPLICATIONS

Fibre is usually recommended as one way of treating haemorrhoids, to minimise constipation and the prolonged straining associated with constipation. Like many recommendations with a long shelf life, there is lots of experience behind this, but few of us could quote the trial evidence. A systematic review [1] tells us both that there is minimal evidence from good quality trials, and that such evidence that exists suggests that fibre is helpful.

## Systematic review

Searching (to early 2005) was excellent. As well as searching many databases, authors contacted companies, experts, and authors. Included studies had to be randomised studies of fibre of any type or dose versus placebo or no therapy in patients with symptomatic haemorrhoids. Outcomes sought included symptomatic improvement, bleeding, prolapse, and surgery, together with any adverse events.

## Results

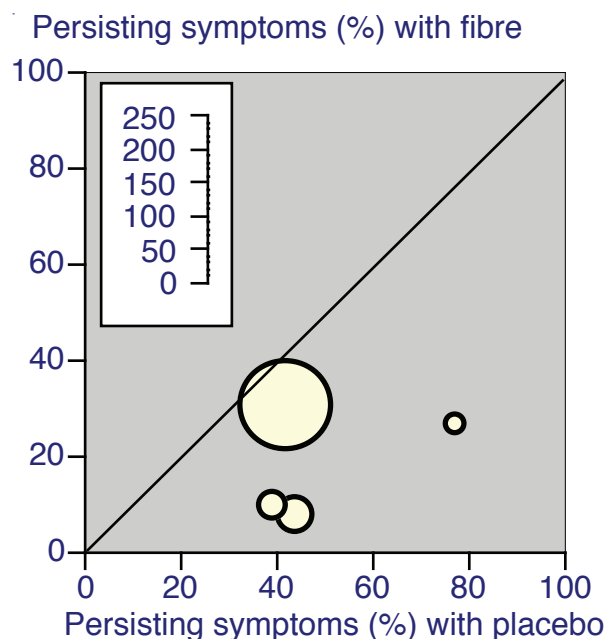
Although seven trials were included, only four provided information on outcomes and were unambiguously randomised and double blind. Most patients presented with rectal bleeding as their main complaint. The duration of studies was up to 12 weeks, and three different forms of fibre were used in the four trials. The number of patients was small, at about 250 in total.

Results for the main outcomes are shown in Table 1. The number of patients with persisting symptoms (Figure 1) or bleeding was reduced by half with fibre compared with placebo (relative risk 0.5; 95% confidence interval 0.4 to 0.7). With placebo, 46% of patients still had persisting symptoms at the end of the study, while with fibre this was reduced to 23%. The number needed to treat for one more patient to be free of symptoms or bleeding was about 4, both for persistence of symptoms or rectal bleeding. There was no difference in prolapse. There was no significant increase in mild adverse events.

## Comment

Fibre is generally used in patients with less severe haemorrhoids. The evidence we have is reasonable, though a concern is that the largest of the trials is the one with the

**Figure 1: Persistence of symptoms in patients with established haemorrhoids treated with fibre or placebo**



smallest effect (Figure 1). The dearth of trials and patients means we can only be reasonably sure that fibre is helping, despite the statistical significance.

There are considerable unknowns. We do not know how big the effect of fibre is, the best fibre product, nor the most appropriate dose of that product. Nor can we be sure, with this number of patients, about common adverse events, and especially about rare, but possibly more serious, adverse events. What we know best is what we do not know.

We do, though, have a wealth of clinical experience to draw on, and in this case that wealth of clinical experience from clinical practice is supported by limited evidence from clinical trials. Getting more fibre or whole grain into the diet is an important healthy living message, and not just for constipation and haemorrhoids. Eating more than four servings of whole grain every week reduces rates of some cancers by 20%-50% (Bandolier 53). A major health message.

Reference:

- 1 P Alonso-Coello et al. Fiber for the treatment of hemorrhoids complications: a systematic review and meta-analysis. American Journal of Gastroenterology 2006 101: 181-188.

**Table 1: Outcomes from systematic review of randomised trials of fibre versus placebo in patients with established troublesome, mostly bleeding, haemorrhoids**

Outcome	Number of		Percent with outcome		Relative risk (95% CI)	NNT (95%CI)
	Trials	Patients	Fibre	Placebo		
Persisting symptoms	4	251	23	46	0.5 (0.4 to 0.7)	4.4 (2.9 to 8.7)
Bleeding	4	253	25	50	0.5 (0.4 to 0.7)	3.9 (2.7 to 7.2)
Prolapse	3	223	26	31	0.8 (0.6 to 1.3)	not calculated

# SPONTANEOUS VIRAL CLEARANCE OF HEPATITIS C

It is one of the minor miracles of life that stuff happens, good as well as bad. Good and bad things happen when sick people are taking a medicine. Good and bad things happen when sick people are not taking a medicine. Some people get better without any outside help or interference. Therein lies the part of the problem of understanding evidence: it isn't about whether good or bad things happen, but whether they happen more or less often, and in whom.

Hepatitis C is devoutly to be avoided, but if you have the virus, it can, in some people, be cleared without any outside help. A systematic review [1] tries to explore whether there is an underlying rate at which the virus is cleared, and some of the problems.

## Systematic review

A relatively simple MEDLINE search sought studies that were longitudinal assessments of hepatitis C infection, with at least one follow up assessment within two years of diagnosis, RNA measurements for virus reported for all study subjects, and studies in patients untreated for acute hepatitis C infection during follow up. Studies that included treated and untreated were included where results for untreated individuals were reported separately.

Clearance of infection was defined on a universally applied basis of hepatitis C RNA assessment, whatever criteria had been used in the original article.

## Results

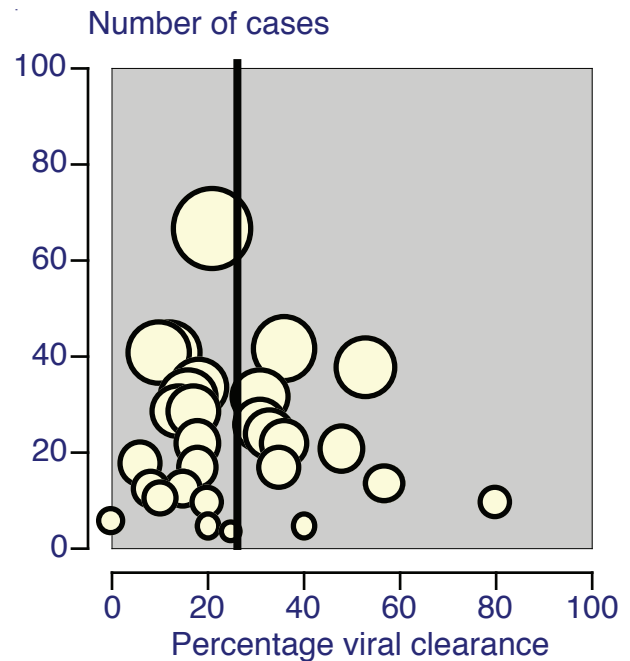
Studies included 19 series of acute hepatitis C, nine of post-transfusional hepatitis C, and three of sero-incident cases. Studies ranged from four to 67 individuals, with an average of 22 per study (682 individuals). Follow up ranged from six to 157 months. The time at which clearance was measured was between six and 48 months, but most were 12 months or longer.

Clearance rates varied from 0% to 80% (Figure 1); there was greater variation in smaller studies. Overall the clearance rate was 26%, and the largest study with 67 individuals was close to this. Studies of acute hepatitis C had a higher rate of spontaneous clearance (31%) than post-transfusional studies (18%). Women had a higher clearance rate (42%) than men (20%).

## Comment

First, it is comforting to know that bad things can clear up on their own accord, and a timely reminder that our bodies can have sufficient natural defences to overcome all sorts of nasty things. Marvellous thing, evolution. Second, it is nice to know that natural laws keep on working: here it was the random play of chance in tiny studies, with the greatest variability in clearance rates seen in studies with fewer than 20 individuals.

Figure 1: Percentage of patients with viral clearance according to size of study - larger symbols represent larger studies



But no real aggregation around the mean was occurring in most of the studies, and larger ones would be needed to be sure of this result. Even at studies of 40 people there was considerable variability, between 10% and 50%. The best current guess is that spontaneous clearance of hepatitis C virus will have occurred in about 1 in 4 people infected with it after a year or more.

There is also a lesson here about small trials. What we are looking at in this study is the equivalent of a placebo group in a clinical trial – what happens when we use an inactive treatment. But in this case there was no placebo, and no reason to magic up a “placebo effect”. If the “placebo effect” was low, any therapy might look brilliant (50% clearance versus 10%, say), but if the “placebo effect” was high, any therapy would probably look ineffective. So much of the evidence we see depends on small numbers that it can be worrying.

Reference:

- 1 JM Micallef et al. Spontaneous viral clearance following acute hepatitis C infection: a systematic review of longitudinal studies. *Journal of Viral Hepatitis* 2006 13: 34-41.

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